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Translation

PATENT COOPERATION TREATY

PCT/DE2003/004114

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P174702PC-La	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DE2003/004114	International filing date (*day/month/year*) 08 December 2003 (08.12.2003)	Priority date (*day/month/year*) 06 December 2002 (06.12.2002)
International Patent Classification (IPC) or national classification and IPC C12N 15/11, 9/12, A61K 48/00		
Applicant TECHNISCHE UNIVERSITÄT DRESDEN		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand 06 July 2004 (06.07.2004)	Date of completion of this report 19 August 2005 (19.08.2005)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DE2003/004114

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed

☒ the description:

pages _____
pages 1-29, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:

pages _____
pages 1-27, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the drawings:

pages _____
pages 1/5-5/5, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL [redacted] LIMINARY EXAMINATION REPORT

[redacted]ernational application No.
PCT/DE2003/004114

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 13-27

because:

☒ the said international application, or the said claims Nos. see supplemental sheet relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III.1

Non-establishment of opinion regarding novelty, inventive step and industrial applicability

Claims 13 to 27 relate to subject matter which, in the opinion of this Authority, falls under PCT Rule 67.1(iv). Consequently, no expert opinion has been established in respect of the industrial applicability of the subject matter of said claims (PCT Article 34(4)(a)(i)).

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/DE 03/04114

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	2, 4, 6-27	YES
	Claims	1, 3, 5	NO
Inventive step (IS)	Claims		YES
	Claims	1-27	NO
Industrial applicability (IA)	Claims	1-12	YES
	Claims		NO

2. Citations and explanations

1. Subject matter of the application

The present application provides antisense constructs against the catalytic subunit of the human telomerase reverse transcriptase (hTERT). As suitable target regions, two segments (nucleotides 2176-2250 and 2296-2393) are identified on the hTERT mRNA.

2. Documents

This report makes reference to the following documents:

D1: WO 01/88198 A (MONIA BRETT P; FREIER SUSAN M (US); GAARDE WILLIAM A (US); ISIS PHARM) 22 November 2001 (2001-11-22)

D2: WO 99/50279 A (LINGNER JOACHIM; ANDREWS WILLIAM H (US); CECH THOMAS R (US); MORIN GR) 7 October 1999 (1999-10-07)

D3: SCHINDLER ASCAN ET AL: "Human telomerase reverse transcriptase antisense treatment downregulates the viability of prostate cancer cells in vitro" INTERNATIONAL JOURNAL OF ONCOLOGY, vol. 19, no. 1, July 2001 (2001-07), pages 25-30, XP002288420

ISSN: 1019-6439

D4: ZHANG Y ET AL: "Effect of antisense hTERT mRNA oligodeoxynucleotide on telomerase activity of leukemic cells" CELL BIOLOGY INTERNATIONAL, vol. 26, no. 5, May 2002 (2002-05), pages 427-431, XP002288421 ISSN: 1065-6995

D5: KOGA S ET AL: "Treatment of bladder cancer cells in vitro and in vivo with 2-5A antisense telomerase RNA" GENE THERAPY, vol. 8, no. 8, April 2001 (2001-04), pages 654-658, XP002288422 ISSN: 0969-7128

D6: SARETZKI GABRIELE ET AL: "Ribozyme-mediated telomerase inhibition induces immediate cell loss but not telomere shortening in ovarian cancer cells" CANCER GENE THERAPY, vol. 8, no. 10, October 2001 (2001-10), pages 827-834, XP002288423 ISSN: 0929-1903

D7: YOKOYAMA YASUHIRO ET AL: "The 5'-end of the hTERT mRNA is a good target for hammerhead ribozyme to suppress telomerase activity" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 273, no. 1, 24 June 2000 (2000-06-24), pages 316-321, XP002288424 ISSN: 0006-291X

D8: SCHERR MICHAELA ET AL: "RNA accessibility prediction: A theoretical approach is consistent with experimental studies in cell extracts" NULCEIC ACIDS RESEARCH, vol. 28, no. 13, 1 July 2000 (2000-07-01), pages 2455-2461, XP002288425 ISSN: 0305-1048

D9: PATZEL V ET AL: "A theoretical approach to select effective antisense oligodeoxyribonucleotides at high statistical probability" NUCLEIC ACIDS RESEARCH, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 27, no. 22, 15 November 1999 (1999-11-15), pages 4328-4334, XP002134406 ISSN: 0305-1048

D10: WHITE LAURA K ET AL: "Telomerase inhibitors" TRENDS IN BIOTECHNOLOGY, vol. 19, no. 3, March 2001 (2001-03), pages 114-120, XP002288426 ISSN: 0167-7799

D11: KRAEMER KAI ET AL: "Antisense-mediated hTERT inhibition specifically reduces the growth of human bladder cancer cells." CLINICAL CANCER RESEARCH: AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH. 1 September 2003, vol. 9, no. 10, Pt 1, 1 September 2003 (2003-09-01), pages 3794-3800, XP002288427 ISSN: 1078-0432

D11 is a P,X document. This document represents prior art that is relevant to the present claim 1 because no support for the two target sequence regions of 2176 to 2250 and 2296 to 2393 could be found in the priority documents.

3. Novelty (PCT Article 33(2))

3.1 P,X document D11 discloses a number of antisense oligonucleotides (AS-ODN) which interact with the target regions defined in claim 1 (see table 1 in D11). Since claim 1 does not enjoy priority (see above), claim 1 is therefore not novel over D11.

3.2 According to claim 3, the target sequence region of the interacting polynucleotides can be modified (by means of addition, amplification, inversion, missense mutation, nonsense mutation, point mutation, deletion and/or substitution). The extent of this modification is not limited, and basically **any imaginable** sequence can therefore be regarded as a target sequence region (because it can be derived from the target sequences defined in claim 1 by means of the specified

modifications). Thus any imaginable polynucleotide sequence which specifically interacts with any other mRNA (such as the antisense and ribozyme constructs of D1-D7) is therefore also covered by the scope of claim 3. Consequently, the subject matter of claim 3 is not novel within the meaning of PCT Article 33(2).

3.3 A similar objection applies to claim 5, which relates to a derivative of a nucleic acid construct. Since neither the type nor the extent of derivitization is defined more precisely, polynucleotides with an amended sequence can also be defined as derivatives within the meaning of the claim. In turn, the constructs of D1-D7, for example, can therefore be regarded as prejudicial to novelty.

4. Inventive step (PCT Article 33(3))

4.1 Documents that describe antisense or ribozyme constructs directed against the hTERT mRNA are considered to be the closest prior art (i.e. D1-D4, D6 and D7).

Proceeding from this prior art, the problem to be solved by the present application is that of identifying especially suitable sequence segments (within the hTERT mRNA) that lead to the provision of more efficient antisense (or similar) constructs.

However, at the time of this application, a person skilled in the art was familiar with methods with which secondary structures of RNA molecules could be successfully predicted. Thus accessible segments in these molecules could be reliably identified (see, for example, D8 and D9).

Hence the identification of such segments **within the hTERT mRNA** cannot be regarded as involving an inventive step, and the subject matter of claims 1 to 12 is therefore not inventive (this subject matter is nothing more than a combination of the teachings of D1 to D7, and D8 and D9).

Furthermore, antisense oligonucleotides directed against hTERT have already been described in a therapeutic context (see D3, D4 and D6), and claims 13 to 27 therefore also do not involve an inventive step within the meaning of PCT Article 33(3).

4.2 The application should also note that the claimed technical effect (**improved** antisense constructs) has not been achieved across the entire scope of claim 1. Figure 2, for example, shows that AS-ODN Ast2186 has similarly moderate efficiency as antisense constructs from other regions of the hTERT mRNA.

5. Further defects in the application

5.1 Sufficient disclosure (PCT Article 5)

Claim 1 relates to all imaginable polynucleotides that specifically interact with the defined target sequences. Since a structural characterization of these polynucleotides has been omitted, the constitution of such polynucleotides (their components, sequence, etc.) is not, with the exception of the antisense and ribozyme constructs, clear to a person skilled in the art. This insufficient disclosure contradicts PCT Article 5.

5.2 Clarity (PCT Article 6)

The application fails to meet the requirements of PCT Article 6 for the following reasons:

a) Claim 1 relates to target sequence ranges 2176 to 2250 and 2296 to 2393 according to the accession number AF015950. However, the database (GenBank, EMBL?) to which this accession number corresponds has not been specified.
Furthermore, it is not clear what the numbers refer to (nucleotide positions, codons?).

b) The length of the polynucleotides is entirely undefined.

c) Target sequence regions 2183-2205 and 2324-2346 (claim 2) are not sufficiently supported in the description. There is no experimental data (see figures) for either region and it is not discernible why precisely these subregions have been selected. In particular 2183-2205 does not appear to be a particularly suitable target sequence in light of figure 2 (compare the neighboring ASt2186).

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: